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REMARKS/ARGUMENTS

Reconsideration and allowance of the present application based on the following remarks are respectfully requested. Upon entry of the above amendments, claims 23-25 and 27-33 as amended, will be pending.

Claims 23-25 and 27-33 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Vitti *et al.* in view of Harlow *et al.* or Nicholson *et al.* or Morgenthaler. In addition, these claims also stand rejected under §103(a) as unpatentable over US 5,614,363 in view of Vitti *et al.*, Harlow *et al.*, and Nicholson *et al.* or Morgenthaler *et al.* The Applicants respectfully traverse these rejections for at least the following reasons.¹

The presently claimed invention provides methods for determination of TSH receptor autoantibodies comprising reacting a biological sample with a solid phase having an affinity-purified immobilized functional recombinant human TSH receptor which is immobilized to the solid support by a selective monoclonal antibody that recognizes only conformation epitopes of human TSH receptor. The Applicants have already described many of the advantages such solid phase techniques, and even that prior attempts at immobilizing such TSH receptors have met with failure. The Examiner contends, however, "that the features upon which applicant relies (i.e., functional TSH receptor, functional receptor fragment) are not recited in the rejected claims...[and] that the selective antibody against the human TSH receptor in claims 23-32 is *any* antibody that binds to human TSH receptor and not functional human TSH receptor."² Although believed to be unnecessary, the Applicants have made the above amendments to expedite prosecution, and believe that the claims are free of the art.

Specifically Vitti *et al.* does not discuss an affinity-purified immobilized functional recombinant human TSH receptor immobilized to a solid support by a selective monoclonal antibody that recognized only conformational epitopes of human TSH receptor. Indeed, the TRAK assay referred to by the Examiner,³ as having "immobilized porcine TSH-receptor to a plate", is still a TSH receptor *in solubilized form*, as seen on p. 55, right hand column, of Vitti

¹ Applicants also formally reiterate their previous arguments presented in their response dated February 2, 2004.

² Office Action mailed July 28, 2004, page 7.

³ Office Action mailed July 28, 2004, page 3.

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which states "the TSH receptor is contained in a solubilized membrane preparation." This inadequacy is not addressed by any of the secondary references.

Finally, with regard to US 5,614,363, the Examiner refers to Col. 7, lines 8-63 and Col. 8, lines 3-11 outlining competitive binding assays employing radiolabeled TSH and TSH receptor. Regarding the discussion in Col. 7, the '363 patent proposes a purification strategy for the TSH receptor protein comprising several solubilization and affinity chromatography steps. A TSH receptor protein which undergoes such purification steps does not retain its functionality (if the purified recombinant TSH receptor was a functional TSH receptor at all – which depends, *inter alia*, from the cells used for its expression).

Regarding the passage at Col. 8, this discussion *at best* suggests only a use of the assay, but hardly enables a skilled artisan to develop a useful solid phase assay for the detection of the claimed antibodies in serum or plasma samples of patients. It is noted that conventional assays, at the time of the '363 patent, used solubilized porcine TSH receptors almost exclusively. Therefore, this discussion could not fairly be cited as evidence of a suggestion of the solid phase techniques of the present invention.

Accordingly, for the above reasons, the Applicants respectfully request the withdrawal of all outstanding rejections under §103(a).

Therefore, all objections and rejections having been addressed, it is respectfully submitted that the present application is in a condition for allowance and a Notice to that effect is earnestly solicited.

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Should any issues remain unresolved, the Examiner is encouraged to contact the undersigned attorney for Applicants at the telephone number indicated below in order to expeditiously resolve any remaining issues.

Respectfully submitted,

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